

Please add the following new claims:

28. The method as recited in claim 4, wherein the step of redetermining the electronic status further comprises amplifying an electronic signal created when the semiconductor is subjected to energy influx.

29. The method as recited in claim 4 wherein the molecules are electron donators.

30. The method as recited in claim 4 wherein the molecules are electron acceptors.

31. The method as recited in claim 18, wherein the biological molecule extracts electrons from the ~~semiconductor~~ ^{semiconductor}.

32. The method as recited in claim 18, wherein the biological molecule donates electrons to the ~~semi-conductor~~ ^{semiconductor}.

33. The method as recited in claim 18, wherein a bidentate moiety is intermediate to the ~~semi-conductor~~ ^{semiconductor} and the biological molecule.

34. The method as recited in claim 18, wherein the ~~semi-conductor~~ ^{semiconductor} is between 1 and 20 nanometers in diameter.

REMARKS

The Examiner requests a proper information disclosure statement under 37 CFR 1.98(b). The Applicants respectfully submit such a statement, herewith.

The drawings are objected to as failing to comply with 37 CFR 1.84(p)(5)

because they included the following reference signs not mentioned in the description: 60 in Figure 3. Per Examiner's request, the Applicants have amended the specification to add the reference sign in the description.

The disclosure is objected to due to minor informalities. The Applicants have amended the specification in accordance with the Examiner's suggestions.

Claims 1-3, 6, 12, 15, and 19 are rejected under 35 U.S.C. 102(b) as being anticipated by Weiss et al. (5,990,479) ("Weiss"). Claims 22-24 are rejected under 35 U.S.C. 102(a) as being anticipated by Bawendi et al. (6,306,610) ("Bawendi").

Claims 8-11, 13, and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Weiss in view of Wood et al. (5,965,877) ("Wood"). Claims 16 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Weiss in view of Meade et al. (5,591,578) ("Meade"). Claim 20 is rejected under 35 U.S.C. 103(a) as being unpatentable over Weiss in view of Han et al. (6,043,428) ("Han"). Claim 5 is rejected under 35 U.S.C. 103(a) as being unpatentable over Weiss in view of Rosen et al. (6,125,529) ("Rosen").

Claim 25 is rejected under 35 U.S.C. 103(a) as being unpatentable over Bawendi in view of Haddon et al. (6,331,262) ("Haddon"). Claims 26 and 27 are being rejected under 35 U.S.C. 103(a) as being unpatentable over Bawendi in view of Uber, III et al. (6,414,318) ("Uber").

Claims 4, 7, 18, and 21 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Allowance of the application is respectfully requested in view of the foregoing amendments and the following remarks. Applicants have rewritten claims 4,7,18, and 21 to include the limitation of their base claims. Allowance of these claims is respectfully solicited.

Independent claims 1, 12, 22 have been amended to recite "subjecting the semiconductor to energy influx sufficient to produce a charge pair separation on the semicon-

ductor's surface" and "prolonging the charge separation via a semiconductor surface-modifier molecule. Support for the added limitations can be found in the specification at, for example, page 5, line 28 (surface modifier), and page 3, lines 27-29 (prolonging).

Claim 1 has been further amended to recite the generation and amplification of an electronic signal. Support for this added limitation is found on page 6, lines 21-27.

Claims 4, 7, 18, and 21 have been changed to independent claims reciting all limitations of their base claims. Applicant appreciates the Examiner's intent to allow these claims.

Claim 28 has been added to depend from previously objected to claim 4. Claim 28 recites the electronic signal amplification limitation discussed supra.

Claims 29-34 have been added to depend on now independent claims 4 and 18. These claims are virtually verbatim recitations of original claims 9-11, 13-15, and 19.

Applicant's invention

The invention provides a method for detecting molecules via the charge separation abilities of semiconductors. A feature of the invention is the utilization of a semiconductor surface-modifying molecule to prolong charge separation on the semiconductor's surface. This feature allows the charge differential to be measurable with existing time-resolved detection systems. The art of record neither anticipates nor suggests the use of surface-modifying molecules to prolong charge separation.

Weiss neither anticipates nor suggests prolonging charge separation on a semiconductor

Claims 1-3, 6, 12, 15, and 19 are rejected under 35 U.S.C. 102(b) as being anticipated by Weiss. Reconsideration of the claims is requested in light of the foregoing amendments and the following remarks.

First, Weiss was initially divulged by the Applicants on page 2, line 14 of the instant specification for teaching the use of simple fluorescence. As noted on page 6, lines 21-27 of the specification, a drawback to fluorescence systems is that their optical signals cannot be magnified, unlike electronic signals. Electronic signals are now

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recited as a new limitation in claim 1.

Second, a salient part of the method recited in claims 1 and 12 is "establishing electronic communication *between* target molecules and a semiconductor." In Weiss, no electronic communications are established *between* the molecules to be detected and the semiconductor. The lines in Weiss referred to by the Examiner do not suggest establishing electronic communication between molecules, but rather those lines discuss various sources of electromagnetic radiation used for detection purposes (Weiss, col. 9, lines 15-55). Weiss discloses the use of *luminescence*, which is the result of an electron emitting a photon upon relaxation back to the unexcited state, *within the same material*.

Unlike Weiss, the instant invention (claim 12) provides for electron shuttling from a genetic material to a semiconductor, i.e., between different materials.

Lastly, Weiss does not anticipate or suggest prolonging charge separation on the semiconductor's surface with a semiconductor surface-modifier molecule, as is now claimed in independent claims 1, 12, and 22.

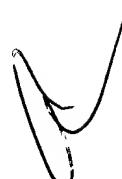
In light of the foregoing, the Applicants submit that claims 1-3, 6, 12, 15 and 19 are patentable over Weiss. Withdrawal of the 35 U.S.C. §102(b) rejection and allowance of the claims is respectfully solicited.

Claims 22-24 are allowable over Bawendi

Claims 22-24 are rejected under 35 U.S.C. 102(a) as being anticipated by Bawendi. Applicants disagree.

Similar to Weiss *supra*, Bawendi utilizes fluorescent nanoparticles and does not disclose semiconductors capable of charge separation or regulation of this charge separation via electron donors or acceptors. See, e.g., Bawendi, col. 4, lines 16-18 ("location and nature of the association can be detected by monitoring the emission of the semiconductor nanocrystal.").

No electronic monitoring occurs between target molecules and semiconductors in Bawendi. Rather, like Weiss, Bawendi utilizes a static fluorescing agent, its



fluorescence not dependant on what attaches to it.

Also, Bawendi does not anticipate or suggest the now recited surface-modifier molecules to prolong charge separation.

In light of the foregoing, Applicants submit that claims 22-24 are patentable over Bawendi. Withdrawal of the 35 U.S.C. §102(b) rejection and allowance of the claims is respectfully solicited.

Wood Does Not Teach Discrete
Donor/Acceptor Moieties

Claims 8-11, 13 and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Weiss in view of Wood. Claims 8-11 depend on claim 1.

In light of the traversal to Weiss, Applicants submit that this rejection is not applicable.

Wood is being cited apparently for its disclosure of electron donors/acceptors. However, it is noteworthy that Wood's "donors" and "acceptors" is merely the semiconductor's internal structure, namely the valence band and conductive band.

This contrasts with the instant method (both claims 1 and 12) which recites a donor/acceptor entity (a surface-modifying molecule) separate from the semiconductor particle.

In light of the foregoing, Applicants submit that the rejection of claims 8-11, 13 and 14 per 35 U.S.C. 103(a) is obviated. Withdrawal of said rejection and allowance of the subject claims is respectfully requested.

Meade Uses Electron Donors/Acceptors
To Speed Up Electronic Transfers

Claims 16 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Weiss in view of Meade. In light of the amendments to independent claim 12, discussed supra, the proposed combination does not anticipate the method as now claimed.

In addition, it should be noted that Meade is designed to speed up electron

transfer between a *plurality* of acceptors and donors. (See Meade's Column 8, lines 24-28 and Column 9, line 1). This is vastly different from the instant method whereby charge separation is prolonged via the utilization of a single surface-modifying molecule which can serve as a donor/acceptor.

Modifying Meade to contain one electron donor/acceptor molecule would obviate the reason for Meade, which is namely to speed up electron transfer along a bulky double-helix molecule.

Furthermore, Meade's enhanced electron transfer is measured at the two "poles" of Meade's construct, the construct comprising an electron acceptor, an electron donor, and the double-helix molecule separating the two. The elimination of one of Meade's electron handling molecules (so as to arrive at the instant-recited invention) would render Meade useless.

If a prior art reference is cited that requires some modification in order to meet the claimed invention and such modification destroys the purpose of the invention disclosed in the reference, one of ordinary skill in the art would not find reason to make the proposed modification. In re Gordon 733 F. 2d 900 (Fed. Cir 1984).

In light of the foregoing, Applicants submit that claims 16 and 17 are patentable in view of Weiss, taken with Meade. Withdrawal of the 35 U.S.C. §103(a) rejection and allowance of the claims is respectfully solicited.

Claim 5 is rejected under 35 U.S.C. 103(a) as being unpatentable over Weiss in view of Rosen. Claim 20 is rejected under 35 U.S.C. 103(a) as being unpatentable over Weiss in view of Han. In light of the instant traversal of Weiss, Applicant's request withdrawal of this rejection based on these secondary references.

Claim 25 is rejected under 35 U.S.C. 103(a) as being unpatentable over Bawendi in view of Haddon. Claims 26 and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bawendi in view of Uber. In light of the instant traversal of Bawendi, Applicants request withdrawal of this rejection based on these secondary references.

Applicants submit that in light of the foregoing amendments and remarks herein,



In re Rajh, et al. (S.N. 09/606,429)
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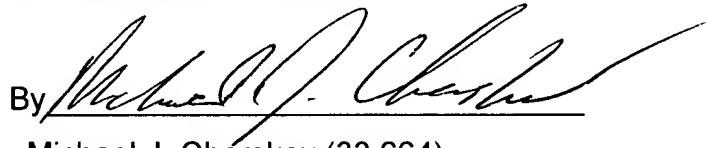
the application is deemed in order for allowance.

An earnest attempt has been made hereby to respond to the §102 and §103 rejections contained in the December 19, 2002 Official Action. Applicants submit that the instant amendment places the application in condition for allowance. If the Examiner feels that a telephonic interview will expedite allowance of the Application, she is respectfully urged to contact the undersigned. Reconsideration and allowance of claims 1-27 and allowance of newly added claims 28-34 is hereby solicited.

Respectfully submitted,

CHERSKOV & FLAYNIK

By


Michael J. Cherskov (33,664)



protein chemistry in vitro and in vivo. In one specific example, surface modification of nanocrystalline metal oxide particles with ortho substituted hydroxylated aromatic ligands was found to result in bidentate coordination of surface Ti atoms. Due to specific bindings of surface modifiers, the optical properties of the small titania particles change with absorption shifting to the red, compared to unmodified nanocrystallites (for salicylate 0.8 eV, ascorbate 1.6 eV and dopamine 1.85 eV). The binding is exclusively characteristic of small particle colloids in the nanocrystalline domain and was found to be a consequence of adsorption induced reconstruction of the nanoparticle surface.

A) A salient feature of the invention is the enhanced charge separation and improved optical properties of nanocrystalline semi-conductors that involve photoinduced interfacial electron transfer from surface modifiers into one or more regions of the semi-conductors. The charge pairs are instantaneously separated into two phases, the holes on the donating organic modifier and the donated electrons in either the conduction band or valence band of the semi-conductor.

Surface modifications of the nanocrystalline particle with bidentate ortho-substituted hydroxylated electron donating ligands, combined with laser excitation of the modified particle, causes a protracted electron decoupling from surface moieties resulting in a correlated radical pair electron spin mechanism, reminiscent of the ion cascade seen in optimized natural photosynthetic systems.

The invention exploits the electrochemical cell characteristics of particulate semiconductors. Inasmuch as the detection system is based on charge separation, the presence or absence of such charge separation (indicative of the presence of certain target moieties), can be measured electronically.

Furthermore the electronic signals generated by this separation can be amplified, thereby providing a sensitivity of the detection system that is superior to those systems relying on typical fluorescence protocols.

It should be noted that a myriad of semiconductors can be utilized to produce the detection device. Titania is depicted herein merely for the sake of

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process. When additional molecules are attached to these modifiers (for example when DNA is attached to the modifier Dopamine 74, as depicted in FIG. 5) the cascade may be protracted. When electron extraction molecules are attached to the DNA (i.e. certain proteins), the cascade maybe blocked, resulting in no absorbance shift or change in electronic state on the surface of the particle 13.

Electron Paramagnetic Resonance (EPR) has shown that electrons which have been energized to the conduction band, are trapped as reduced metal centers; in the case of TiO_2 the electrons facilitate reduction of Ti (IV) to Ti (III). Concomitantly, the holes left in the valence band are trapped as oxygen centered radicals covalently linked to surface titanium atoms. A schematic diagram of this phenomenon is provided as FIG. 2.

A particle-biological molecule construct has been invented, and is the product of an electrophilic reaction between the carboxylic terminus of oligonucleotide and amino-containing electrophilic reagents, the reaction depicted generally as numeral 50 in FIG. 3. In the illustrated embodiment, a semiconductor particle (preferably one having octahedral structure, such as TiO_2) 13 is bound to oligonucleotide(s) 58 via a charge-transfer intermediary. This is accomplished by a series of electrophilic and nucleophilic substitutions.

In a first step, depicted as Roman Numeral I in FIG. 3, the oligonucleotide 58 is modified at its carboxylic terminus to contain an ester-moiety. First, the carboxyl terminus is transformed into a succinimide intermediate via extraction of the hydroxyl moiety. Then, in a nucleophilic substitution, the succinimide group is expelled and its place taken by a basic amino group 56 (a suitable amino group found on N-hydroxy-succinimide, as shown) to form an oligo nucleotide with an ester terminus 57.

The ester terminus reacts with one or a plurality of bidentate or tridentate modifiers 54 in reaction sequence II of FIG. 3, to arrive at the oligo-bidentate construct 53 or constructs. As depicted in sequence III, the construct 53 then

contacts a nanocrystalline particle 13 of suitable geometry to form the particle-modifier-oligo construct 60. Alternatively, the modifier 54 can already be attached to the particle prior to joining with the oligo-ster terminus 57.)

5 One suitable class of modifiers are the 1,2 dihydroxyl phenyls, an exemplary species being dopamine. Generally, when oligonucleotides or PNAs are to be ultimately connected to the nanocrystalline particles, the intermediate modifier particles contain amino moieties. The modifiers are strongly coupled to the surface of the nanocrystalline titanium dioxide particles 13.

10 Additionally, titanium dioxide nanoparticles are bound to proteins, peptide nucleic acids (PNAs) or oligonucleotides. Generally, the particles are coupled to bidentate modified 1,2 dihydroxyl benzoic acids when proteins ultimately are to be complexed with the particles via an intermediate N-hydroxy-succinimide ester in a similar reaction sequence as that depicted in FIG. 3.

15 The remaining particle surface is protected to prevent undesirable reactions of hydroxyl groups at the titanium surface with carboxyl and phosphodiester groups on the oligo. An exemplary means for protecting the surface is a layer of glycidyl isopropyl ether on the semi-conductor's surface. Generally, any material which removes or otherwise blocks hydroxyl moieties on the titania surface from reacting with target molecules is suitable. In the case of the glycidyl isopropyl ether, a layer approximating 5 angstroms (\AA) in thickness is suitable.

20 A salient feature of the invented process is the observation of a red-shift which results when certain modifiers are present on nano-sized semi-conductor particles. Specifically, and as depicted in FIG. 4, unmodified TiO_2 particles 13 exhibit absorbency at approximately 400 nm. However, when modifier moieties (such as dopamine, 74) are attached to the particle, the resulting construct 72 exhibits a shift in absorbency to a longer wavelength of approximately 600 nm.

25 The absorption in the red region reflects the presence of the excess electrons in the excited state of TiO_2 and is due to the absorption of localized and delocalized electrons (Ti(III)) in TiO_2 . The shape of this part of the spectrum

protein chemistry in vitro and in vivo. In one specific example, surface modification of nanocrystalline metal oxide particles with ortho substituted hydroxylated aromatic ligands was found to result in bidentate coordination of surface Ti atoms. Due to specific bindings of surface modifiers, the optical properties of the small titania particles change ~~which~~ ^{with} absorption shifting to the red, compared to unmodified nanocrystallites (for salicylate 0.8 eV, ascorbate 1.6 eV and dopamine 1.85 eV). The binding is exclusively characteristic of small particle colloids in the nanocrystalline domain and was found to be a consequence of adsorption induced reconstruction of ~~the~~ nanoparticle surface.

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The absorption in the red region reflects the presence of the excess electrons in the excited state of TiO_2 and is due to the absorption of localized and delocalized electrons (Ti(III)) in TiO_2 . The shape of this part of the spectrum

1. (Amended) A method for detecting target molecules, the method comprising:

- a) determining the electronic status of a semi[-]conductor;
- b) establishing electronic communication between the target molecules and the semiconductor;
- c) subjecting the semi[-]conductor to energy influx sufficient to produce a charge pair separation on the semiconductor's surface, thereby generating an electronic signal;
- d) prolonging the charge separation via a semiconductor surface-modifying molecule;
- e) redetermining the electronic status of the semi[-]conductor by amplifying the electronic signal.

10 4. (Amended) A method for detecting molecules, the method comprising:
c) determining the electronic status of a semiconductor;

d) establishing electronic communication between the molecules and the semiconductor:

e) subjecting the semiconductor to energy influx and;
d) redetermining the electronic status of the semiconductor; wherein the semiconductor[s are] is an octahedral metal oxide[s].

14 7. (Amended) A method for detecting molecules, the method comprising:
e) determining the electronic status of a semi-conductor;

b) establishing electronic communication between the molecules and the semiconductor:

c) subjecting the semiconductor to energy influx; and

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d) redetermining the electronic status of the semiconductor, wherein bidentate moieties are positioned intermediate the molecules and the semiconductor, and wherein the moieties are dihydroxyl phenyls selected from the group consisting of 1,2-dihydroxyl phenylamine, 1,2-dihydroxyl phenyl alanine, 1,2-dihydroxyl benzoic acid, 1,2-dihydroxyl glycine, 1,2-dihydroxyl benzyl amine, and combinations thereof.

15 ~~12.~~ (Amended) A method for detecting biological molecules, the method comprising:

- a) supplying a semi[-]conductor having a first energy level and a second energy level and whereby the first energy level corresponds to a first optical characteristic of the semi[-]conductor;
- b) establishing electrical contact between the semi[-]conductor and the molecules;
- c) causing electrons to move from the molecules to the second energy level, wherein a charge separation occurs on the surface of the semiconductor;
- d) using a semiconductor surface-modifying molecule to prolong the charge separation; and
- e) monitoring any change in the first optical characteristic.

23 ~~18.~~ (Amended) A method for detecting biological molecules, the method comprising:

- a) supplying a semiconductor having a first energy level and a second energy level and whereby the first energy level corresponds to a first optical characteristic of the semiconductor;
- b) establishing electrical contact between the semiconductor and the molecules;

c) causing electrons to move from the molecule to the second energy level;

and

d) monitoring any change in the first optical characteristic. [The method as recited in claim 12] wherein the semiconductor[s] are] is an octahedral metal oxide[s].

28 21. (Amended) A method for detecting biological molecules, the method comprising:

a) supplying a semi-conductor having a first energy level and a second energy level and whereby the first energy level corresponds to a first optical characteristic of the semiconductor;

b) establishing electrical contact between the semiconductor and the molecules;

c) causing electrons to move from the molecule to the second energy level, resulting in the formation of an oxidative region on the semiconductor. [The method as recited in claim 20,] wherein the oxidative region facilitates the cleavage of molecules; and

d) monitoring any change in the first optical characteristic.

29 22. (Amended) A method for detecting target moieties *in situ*, the method comprising:

a) binding biological material to nanocrystalline semiconductor particles, wherein the material has an affinity to the target moiety;

b) facilitating entry of the bound material into an organelle; and

c) subjecting the semiconductor to radiation sufficient to produce a charge pair separation on the semiconductor's surface; and

d) using semiconductor surface-modifier molecules to prolong the charge separation.

(initials)

Please add the following new claims:

11 28. The method as recited in claim 4, wherein the step of redetermining the electronic status further comprises amplifying an electronic signal created when the semiconductor is subjected to energy influx.

12 29. The method as recited in claim 4 wherein the molecules are electron donators.

13 30. The method as recited in claim 4 wherein the molecules are electron acceptors.

14 31. The method as recited in claim 18, wherein the biological molecule extracts electrons from the semi-conductor.

15 32. The method as recited in claim 18, wherein the biological molecule donates electrons to the semi-conductor.

16 33. The method as recited in claim 18, wherein a bidentate moiety is intermediate to the semi-conductor and the biological molecule.

17 34. The method as recited in claim 18, wherein the semi-conductor is between 1 and 20 nanometers in diameter.

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